is observed, the dose is the highest dose tested.

Acknowledgment. The authors are indebted to our Analytical Chemistry Department for NMR and IR spectra.

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Prostaglandins and Congeners. 15.[1] Synthesis and Bronchodilator Activity of *dl*-11-Deoxy-15- or 16-alkylprostaglandins

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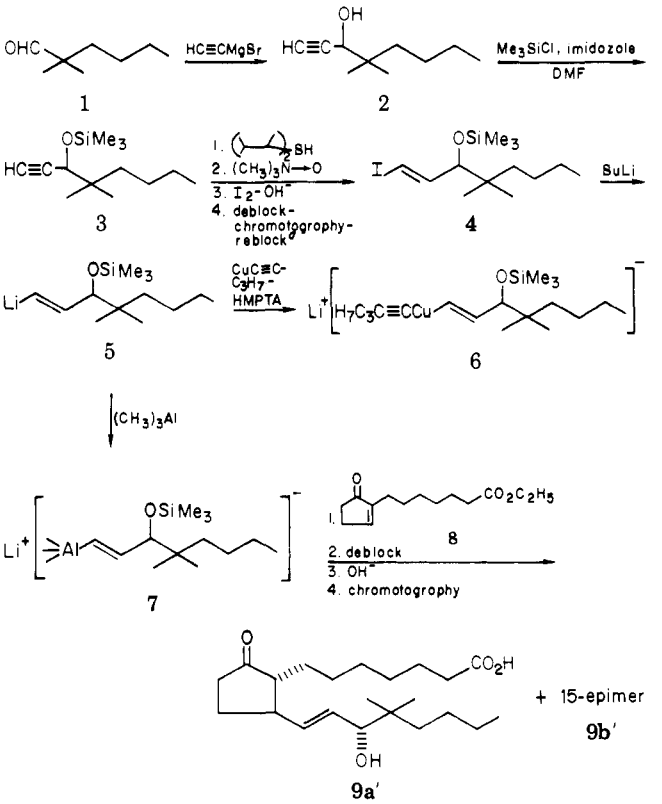
The synthesis of *dl*-11-deoxy-15- or 16-alkylprostaglandins by the conjugate addition of appropriately substituted lithium alanate or lithium cuprate reagents to several cyclopentenones is described as is the preparation of the requisite intermediate (*E*)-1-iodo-1-alkenyl compounds **4**, **22**, **23**, and **31**. The bronchodilator activity of these prostaglandin congeners is presented.

The introduction of alkyl groups at C_{15} or C_{16} in the prostaglandin molecule has provided compounds that are resistant to metabolic inactivation by 15-hydroxyprostaglandin dehydrogenase[2] with resulting enhancement of potency, oral activity at least as inhibitors of gastric acid secretion, and prolongation of effect.[3] Accordingly we were interested in the preparation and biological evaluation of related compounds in the 11-deoxy series, which afford advantages with respect to stability and perhaps also to selectivity of biological effect, a most important consideration. It also was of obvious interest to prepare such compounds in which the α chain (C_1–C_7) would be expected to be resistant to fatty acid β-oxidation,[4] the second major course of prostaglandin metabolic inactivation.[5]

Chemistry. Our synthetic approach utilizes as its key step the facile conjugate addition of an appropriately blocked 3-oxy-3- or 4-substituted (C_{15} or C_{16} in the ultimate prostaglandin) (*E*)-1-alkenyllithium cuprate[1,6] or -lithium alanate[4a] to cyclopentenones. Critical to this approach is the synthesis of the requisite (*E*)-1-alkenyl 1-iodides for the preparation of the organometallic reagent.

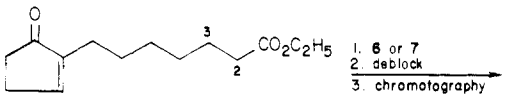
For the 16,16-dimethyl series, the required vinyl iodide **4**[7] was prepared as illustrated in Scheme I. Condensation[8] of aldehyde **1**[9] with acetylenemagnesium bromide afforded alcohol **2**, which was converted to the trimethylsilyl ether **3**. The choice of blocking group is important since hindrance by the adjacent *gem*-dimethyl group increases the stability of the blocked ether. Thus, conditions required for effective deblocking of the more bulky trityl or dimethyl *tert*-butylsilyl ethers were now too vigorous and resulted in at least partial disruption of the allylic 15-hydroxy function and, in the 11-hydroxy series, of the β-ketol function. On the other hand, the usually highly labile trimethylsilyl ether was now sufficiently stable to survive the conditions of conjugate addition. Hydroboration–oxidation–iodination of the acetylene function

Scheme I

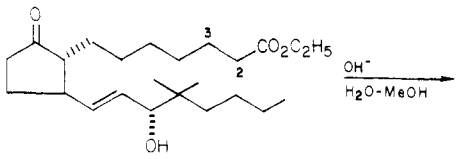


[a] See ref 11.

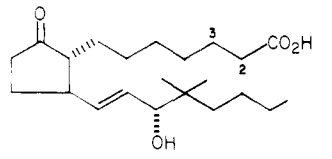
Scheme II



10, 2-Me
11, 2-Ph
12, 3-oxa



13a, 2-Me
b, 2 Me, 15-epi
14a, 2-Ph
b, 2-Ph, 15-epi
15a, 3-oxa
b, 3-oxa, 15-epi



13a′,b′-15a′,b′

of **3** by the procedure of Kluge and co-workers[10] furnished vinyl iodide **4**.[11]

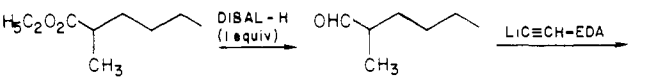
Metallation of **4** with butyllithium provided the corresponding alkenyllithium reagent **5**, which was converted to either the lithium cuprate **6** or lithium alanate **7** by treatment with copper(I) pentyne ($CuC{\equiv}CC_3H_7$)[12]–hexamethylphosphorous triamide (HMPTA)[12b] or trimethylaluminum,[4a] respectively. Submission of **7** to cyclopentenone **8**,[13,14] followed by deblocking, saponification, and dry column chromatography, gave *dl*-11-deoxy-16,16-dimethylprostaglandin E_1 (**9a′**) and its C_{15} epimer **9b′**.[15,16] By analogous procedures, the ethyl esters of the 2-methyl (**13a,b**), 2-phenyl (**14a,b**), both of which are presumably mixtures of C-2 epimers, and 3-oxa (**15a,b**) derivatives of this series were obtained from cyclopentenones **10–12**,[14] respectively, the 2-methyl analogues via **7**, and the others by the cuprate procedure (Scheme II). Alkaline hydrolysis of these 11-deoxy esters afforded the corresponding acids.

For the 16ξ-methyl series (Scheme III), partial reduction of ethyl 2-methylhexanoate (**16**) with diisobutylaluminum hydride (DIBAL-H)[17] provided aldehyde **17**[18] in 77% yield. Treatment of **17** with lithium acetylide–ethylenediamine complex (LiC≡CH·EDA)[19] afforded the propargyl alcohol **18**, which was trimethylsilylated and then converted to the 1-alkenyl 1-iodide **22** by the Kluge diisoamylborane procedure.[10] From vinyl iodide **22**, by the lithium cuprate procedure, *dl*-11-deoxy-16ξ-methylprostaglandin E_1 ethyl ester (**25a**) and *dl*-11-deoxy-16ξ-methylprostaglandin E_2 ethyl ester (**26a**) and their respective C_{15} epimers[15,16] were prepared using cyclopentenones **8**[13,14] and **24**,[20] respectively. Saponification then provided the corresponding acids.[21]

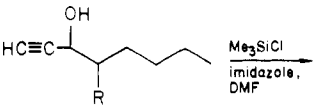
The 16ξ-ethyl derivatives of *dl*-11-deoxyprostaglandin E_1 (**27a′,b′**) and *dl*-11-deoxyprostaglandin E_2 (**28a′,b′**) were similarly prepared (Scheme III). The requisite vinyl iodide **23** was obtained from commercially available 4-ethyl-3-hydroxy-1-octyne (**19**) by trimethylsilylation and hydroiodination.[10]

The synthesis of the *dl*-11-deoxy-15ξ-methylprostaglandins is illustrated in Scheme IV. Addition of methylmagnesium iodide to iodovinyl ketone **29**[10] provided the tertiary alcohol **30** which was protected to give (*E*)-1-

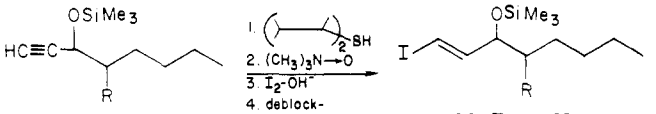
Scheme III



16 17

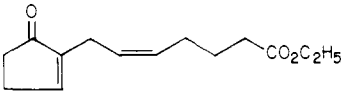


18, R = CH_3
19, R = C_2H_5

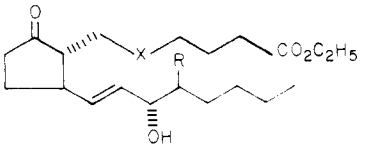


20, R = CH_3
21, R = C_2H_5

22, R = CH_3
23, R = C_2H_5



24



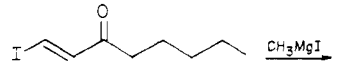
C_{15} epimer

25b–28b

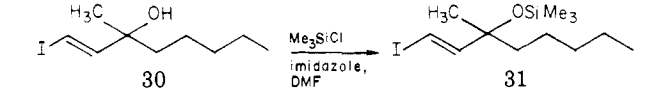
25a, R = CH_3; X = $-CH_2CH_2-$
26a, R = CH_3; X = $-CH{=}CH-$ (cis)
27a, R = C_2H_5; X = $-CH_2CH_2-$
28a, R = C_2H_5; X = $-CH{=}CH-$ (cis)

[a] See ref 11.

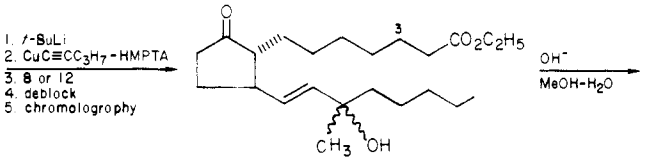
Scheme IV



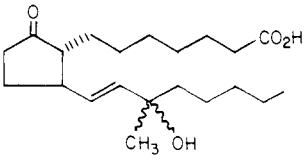
29



30 31



32, 33 (3-oxa)



32′, 33′ (3-oxa)

iodo-3-methyl-3-trimethylsilyloxy-1-octene (**31**). Conjugate addition of the cuprate derived from **31** to cyclopentenones **8**[13,14] and **12**[14] afforded *dl*-11-deoxy-15ξ-methylprostaglandin E_1 ethyl ester (**32**) and *dl*-11-deoxy-15ξ-methyl-3-oxaprostaglandin E_1 ethyl ester (**33**), respectively. For each of these preparations we were unable to effect separation of the 15-epimeric racemates,[22] the presence of which was demonstrated by ^{13}C NMR. Alkaline hydrolysis of **33** and **34** furnished acids **33′**[23] and **34′**, respectively.

Biology. The various 15- and 16-alkyl derivatives were tested as potential bronchodilators by the guinea pig bronchodilator assays[1,24] (see Experimental Section) using the intravenous route against bronchoconstrictions induced by serotonin, histamine, and acetylcholine. The results are summarized in Table I. It is clear from these results that the introduction of one[21] or two methyl groups in the 16 position or of a methyl group to C_{15}[23] is consistent with high potency. However, a *gem*-dimethyl feature at C_{17} leads to significantly diminished activity.[25] In the E_2 series, but apparently not in the E_1 series, a C_{16}-ethyl group results in diminished activity relative to the corresponding 16ξ-methyl congener.

As to modifications of the α chain (C_1–C_7), introduction of a methyl or phenyl group at C_2 was not consistent with activity in this assay. However, replacement of C_3 with oxygen did provide compounds of high potency.

The 15-epi derivatives of the active compounds of this series also appeared to be effective bronchodilators but of diminished potency. With a few exceptions the ethyl esters were significantly less potent than their corresponding acids, due perhaps to poor solubilization or poor resorption.

Despite the good potency displayed by many of these congeners, this series proved uninteresting since these compounds are generally characterized by initial, brief, spasmogenic effects. These latter effects are observed not only in the intravenous guinea pig assays but also with selected examples when administered by aerosol to pilocarpine-bronchoconstricted dogs.[26,27]

Experimental Section

All organometallic reactions were performed under an inert atmosphere of argon or nitrogen. All organic extracts were dried with anhydrous $MgSO_4$ or Na_2SO_4. Solvents were removed under reduced pressure using a Büchi evaporator.

Infrared spectra were recorded with neat samples on a Perkin-Elmer Model 21 spectrophotometer. Proton magnetic resonance spectra were determined in $CDCl_3$ using Varian A-60 or HA-100D spectrophotometers. Chemical shifts are given in parts per million downfield from an internal $(CH_3)_4Si$ standard. Those analytical results indicated by symbol only were within ±0.4% of their calculated values. Mass spectra were recorded on an AEI MS-9 at 70 eV. Only characteristic spectral data are presented for each compound.

General Alanate Conjugate Addition Procedure. Preparation of *dl*-11-Deoxy-16,16-dimethyl-2-methylprostaglandin E_1 Ethyl Ester (13a) and 15-Epimer 13b. To a stirred solution of 27.3 g (60 mmol) of vinyl iodide 4 and 20 mL of anhydrous toluene cooled to −40 °C was added 26.1 mL (60 mmol) of *n*-BuLi (2.3 M in hexanes). The resulting solution was warmed to 0 °C for 3 h and 40 min and then 79.8 mL (60 mmol) of trimethylaluminum (0.75 M in heptane) was added. The reaction mixture was warmed to 20 °C for 30 min, diluted with 20 mL of anhydrous ether, and recooled to 78 °C, and to it was added 15.35 g (60.1 mmol) of 2-(6-carbethoxyhexyl-6-methyl)cyclopent-2-en-1-one (10)[14] and 35 mL of anhydrous ether. The reaction mixture was warmed to ambient temperature, stirred for 24 h, and then poured into a solution of 20 mL of concentrated HCl and 500 g of iced water. After 30 min, the aqueous phase was separated and extracted with ether. The combined organic phases were washed with brine, dried, and concentrated in vacuo to give 30 g of an oil. The oil was applied to a silica gel dry column (3 × 72 in.; 1:9 EtOAc–benzene). The product was isolated from the column to give 6.2 g of an oil. This oil was treated with a solution of 140 mL of acetic acid–THF–water (4:2:1) for 10 min, diluted with xylene, and concentrated in vacuo to give 5.3 g of oil. The oil was applied to a silica gel dry column (2 × 72 in.; 1:4 EtOAc–benzene).

The more polar product **13a**[15,16] was isolated as 1.937 g (8%) of an oil: IR 3700, 1739, and 975 cm^{-1}; ^1H NMR δ 5.63 (m, 2 H, C-13,14 H), 4.11 (q, 2 H, $-OCH_2CH_3$, J = 7 Hz), 3.81 (m, 1 H, C-15 H), 2.30 (m, 1 H, C-2 H), 1.62 (m, 1 H, OH), 1.11 (d, 3 H, C-2 CH_3, J = 7 Hz), 0.90 (t, 3 H, C-20 H), 0.87 and 0.83 (s and s, 6 H, *gem*-dimethyl H). Anal. ($C_{25}H_{44}O_4$) C, H.

The less polar product **13b**[15,16] was isolated as 1.512 g (6%) of an oil: IR 3640, 1739, and 975 cm^{-1}; ^1H NMR δ 5.65 (m, 2 H, C-13,14 H), 4.12 (q, 2 H, $-OCH_2CH_3$, J = 7 Hz), 3.82 (m, 1 H, C-15 H), 2.30 (m, 1 H, C-2 H), 1.62 (m, 1 H, OH), 1.11 (d, 1 H, C-2 CH_3, J = 7 Hz), 0.90 (t, 3 H, C-20 H), 0.83 and 0.81 (s and s, 6 H, *gem*-dimethyl H). Anal. ($C_{25}H_{44}O_4$) C, H.

Also isolated was 0.217 g (1%) of a mixture of **13a** and **13b**.

General Cuprate Conjugate Addition Procedure. Preparation of *dl*-11-Deoxy-16,16-dimethyl-2-phenylprostaglandin E_1 Ethyl Ester (14a) and 15-Epimer 14b. To a stirred solution of 9.28 g (26.2 mmol) of vinyl iodide 4 and 5 mL of dry ether cooled to −78 °C was slowly added 66 mL (52.8 mmol) of *t*-BuLi (0.8 M in pentane). After 1 h, the solution was warmed to −10 °C for 1 h and recooled to −78 °C, and to it was added a solution of 3.50 g (26.8 mmol) of copper(I) pentyne,[12] 11 mL of hexamethylphosphorous triamide (HMPTA),[12b] and 60 mL of dry ether. After 1 h, a solution of 7.99 g (25.4 mmol) of 2-(6-carbethoxyhexyl-6-phenyl)cyclopent-2-en-1-one (11)[14] and 80 mL of dry ether was added. The solution was stirred for 30 min, warmed to −15 °C for 75 min, and poured into 600 mL of saturated NH_4Cl. After vigorous stirring for 2 h the resulting blue solution was extracted with 500 mL of ether in four portions. The combined ether extracts were washed with 1% H_2SO_4 and brine, dried, and concentrated in vacuo to give 13.26 g of brown liquid. A solution of the 13.26 g and 210 mL of acetic acid–THF–H_2O (4:2:1) was stirred at ambient temperature for 20 min, diluted with toluene, and concentrated in vacuo to afford 10.82 g of brown oil. This oil was applied to a dry column of 1200 g of silica gel [3 in. flat × 47 in. packed; EtOAc–benzene (1:9); 300 mL of eluent was collected].

The more polar isomer **14a**[15,16] was isolated from the column at R_f 0.15–0.28 as 2.05 g (17%) of a yellow oil: IR 3600, 1740, 1600, 970, 735, and 700 cm^{-1}; ^1H NMR δ 7.33 (s, 5 H, C_6H_5), 5.63 (m, 2 H, C-13,14 H), 4.13 (q, 2 H, $-OCH_2CH_3$, J = 7 Hz), 3.83 (m, 1 H, C-15 H), 3.53 (t, 1 H, C-2 H, J = 7 Hz), 0.90 (t, 3 H, C-20 H), 0.88 and 0.83 (s and s, 6 H, *gem*-dimethyl H). Anal. ($C_{30}H_{40}O_4$) C, H.

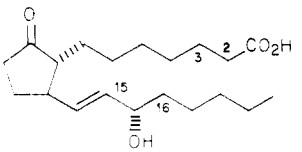
The less polar isomer **14b**[15,16] was isolated from the column at R_f 0.36–0.51 as 3.23 g (27%) of a yellow oil: IR 3600, 1740, 1600, 970, 735, and 700 cm^{-1}; ^1H NMR δ 7.35 (s, 5 H, C_6H_5), 5.67 (m, 2 H, C-13,14 H), 4.13 (q, 2 H, $-OCH_2CH_3$, J = 7 Hz), 3.82 (m, 1 H, C-15 H), 3.50 (t, 1 H, C-2 H, J = 7 Hz), 0.90 (t, 3 H, C-20 H), 0.88 and 0.83 (s and s, 6 H, *gem*-dimethyl H). Anal. ($C_{30}H_{40}O_4$) C, H.

General Saponification Procedure. Preparation of *dl*-11-Deoxy-16,16-dimethyl-2-phenylprostaglandin E_1 (14a′). A solution of the ester and MeOH–H_2O (1:1) containing NaOH or KOH (~6–7 equiv) was stirred at ambient temperature for 24–72 h (for the 2-phenyl derivatives, 7–10 h of reflux were required). The resulting solution was extracted with ether, and the extracts were discarded. The remaining aqueous phase was acidified (5% HCl) and extracted with ether. The combined ether extracts were washed with brine, dried, and concentrated in vacuo to furnish the acid.

Thus, 845 mg (56%) of **14a′** was obtained as an amber oil: IR 3600–3400, 2700–2500, 1740, 1690, 1600, 970, 725, and 695 cm^{-1}; ^1H NMR δ 7.00 (s, 5 H, C_6H_5), 6.43 (m, 2 H, OH), 5.63 (m, 2 H, C-13,14 H), 3.85 (m, 1 H, C-15 H), 3.53 (t, 1 H, C-2 H, J = 7 Hz), 0.90 (t, 3 H, C-20 H), 0.87 and 0.83 (s and s, 6 H, *gem*-dimethyl H). Anal. ($C_{28}H_{42}O_4$) C, H.

4,4-Dimethyl-3-hydroxy-1-octyne (2). (Acetylene was continuously bubbled into the reaction mixture during the entire procedure.) To 300 mL of anhydrous THF, saturated with acetylene, was added dropwise with stirring 156 mL (0.5 mol) of *n*-butylmagnesium chloride (3.2 M in THF) while maintaining the temperature between 20 and 25 °C. The reaction was stirred for 1 h after addition was complete, and then 29.5 g (0.23 mmol) of 2,2-dimethylhexanal (1)[9] in an equal volume of THF was added dropwise. After 1 h, the reaction mixture was poured into an ice-cold saturated NH_4Cl solution. The aqueous phase was separated and extracted with ether. The combined organic phases were washed with brine, dried, and concentrated in vacuo to give a yellow liquid. Distillation afforded 27 g (76%) of **2** as a colorless liquid: bp 47–48 °C (0.8 mm); IR 3509 and 3390 cm^{-1}; ^1H NMR δ 4.10 [m, 1 H, $-CH(OH)-$], 2.45 (d, 1 H, $HC{\equiv}CCH-$, J = 2 Hz), 1.87 (m, 1 H, OH), 0.98 (t, 3 H, CH_2CH_3), and 0.96 (s, 6 H,

Table I. Bronchodilator Activity of *dl*-11-Deoxy-15- or 16-alkylprostaglandins



Compd[a]	α-Chain (C_1-C_7) variant	β-Chain (C_{13}-C_{20}) variant	Yield, %	Formula	Analyses[b]	Guinea pig bronchodilator assays,[c] ED_{50}, g/kg: Serotonin	Histamine	Acetylcholine
dl-11-Deoxy-PGE_1						397 × 10^{-9}	3.4 × 10^{-6}	>32 × 10^{-6}
9a'	None	16,16-Dimethyl	10[d] 19[d,e]	$C_{22}H_{38}O_4$	C, H	25.9 × 10^{-6}	4.17 × 10^{-6}	42.9 × 10^{-6}
9b'	None	16,16-Dimethyl, 15 epi	7[d]	$C_{22}H_{38}O_4$	C, H	19.0 × 10^{-6}	107 × 10^{-6}	135 × 10^{-6}
13a	2ξ-Methyl, ethyl ester	16,16-Dimethyl	8 1[e]	$C_{25}H_{44}O_4$	C, H			
13b	2ξ-Methyl, ethyl ester	16,16-Dimethyl, 15-epi	6	$C_{25}H_{44}O_4$	C, H			
13a'	2ξ-Methyl	16,16-Dimethyl	91[f]	$C_{23}H_{40}O_4$	C, H	g	g	g
13b'	2ξ-Methyl	16,16-Dimethyl, 15-epi	94[f]	$C_{23}H_{40}O_4$	C, H	g	g	g
14a	2ξ-Phenyl, ethyl ester	16,16-Dimethyl	17	$C_{30}H_{46}O_4$	C, H	g	g	g
14b	2ξ-Phenyl, ethyl ester	16,16-Dimethyl, 15-epi	27	$C_{30}H_{46}O_4$	C, H	g	g	g
14a'	2ξ-Phenyl	16,16-Dimethyl	56[f]	$C_{28}H_{42}O_4$	C, H	g	g	g
14b'	2ξ-Phenyl	16,16-Dimethyl, 15-epi	86[f]	$C_{28}H_{42}O_4$	C, H	g	g	g
15a	3-Oxa, ethyl ester	16,16-Dimethyl	7 4[e]	$C_{23}H_{40}O_5$	C, H	123 × 10^{-6}	69.6 × 10^{-6}	96.7 × 10^{-6}
15b	3-Oxa, ethyl ester	16,16-Dimethyl, 15-epi	11	$C_{23}H_{40}O_5$	C, H	209 × 10^{-6}	194 × 10^{-6}	349 × 10^{-6}
15a'	3-Oxa	16,16-Dimethyl	78[f]	$C_{21}H_{36}O_5$	C, H	185 × 10^{-6}	(32 × 10^{-6})[h]	550 × 10^{-6}
15b'	3-Oxa	16,16-Dimethyl, 15-epi	77[f]	$C_{21}H_{36}O_5$	C, H	(32 × 10^{-6})[h]	373 × 10^{-6}	558 × 10^{-6}
25a	Ethyl ester	16ξ-Methyl	4 8[e]	$C_{23}H_{40}O_4$	H; C[i]	(320 × 10^{-9})[h]	(32 × 10^{-9})[h]	g
25b	Ethyl ester	16ξ-Methyl, 15-epi	3	$C_{23}H_{40}O_4$	C, H	99.3 × 10^{-6}	(32 × 10^{-6})[h]	396 × 10^{-6}
25a'[j]	None	16ξ-Methyl	57[f]	$C_{21}H_{36}O_4$	*k*	346 × 10^{-6}	(320 × 10^{-6})[h]	>320 × 10^{-6}
25b'	None	16ξ-Methyl, 15-epi	96[f]	$C_{21}H_{36}O_4$	*k*	7.01 × 10^{-6}	73.2 × 10^{-6}	9.89 × 10^{-6}
26a	PGE_2 series, ethyl ester	16ξ-Methyl	15 2[e]	$C_{23}H_{38}O_4$	C, H	179 × 10^{-9}	65.7 × 10^{-9}	g
26b	PGE_2 series, ethyl ester	16ξ-Methyl, 15-epi	17	$C_{23}H_{38}O_4$	C, H	9.65 × 10^{-6}	1.37 × 10^{-6}	>320 × 10^{-6}
26a'[j]	PGE_2 series	16ξ-Methyl	98[f]	$C_{21}H_{34}O_4$	H; C[l]	1.35 × 10^{-6}	108 × 10^{-9}	1.63 × 10^{-6}
26b'	PGE_2 series	16ξ-Methyl, 15-epi	99[f]	$C_{21}H_{34}O_4$	C, H	39.9 × 10^{-6}	2.99 × 10^{-6}	87.5 × 10^{-6}
27a	Ethyl ester	16ξ-Ethyl	8 18[e]	$C_{24}H_{42}O_4$	C, H	1.11 × 10^{-3}	(32 × 10^{-6})[h]	145 × 10^{-6}
27b	Ethyl ester	16ξ-Ethyl, 15-epi	26	$C_{24}H_{42}O_4$	C, H	1.74 × 10^{-3}	2.70 × 10^{-3}	g
27a'	None	16ξ-Ethyl	87[f]	$C_{22}H_{38}O_4$	C, H	9.77 × 10^{-6}	(32 × 10^{-6})[h]	113 × 10^{-6}
27b'	None	16ξ-Ethyl, 15-epi	95[f]	$C_{22}H_{38}O_4$	H; C[m]	>3.2 × 10^{-6}	(32 × 10^{-6})[h]	g
28a	PGE_2 series, ethyl ester	16ξ-Ethyl	17 9[e]	$C_{24}H_{40}O_4$	C, H			
28b	PGE_2 series, ethyl ester	16ξ-Ethyl, 15-epi	25	$C_{24}H_{40}O_4$	H; C[n]			
28a'	PGE_2 series	16ξ-Ethyl	80[f]	$C_{22}H_{36}O_4$	C, H	79.1 × 10^{-6}	g	g
28b'	PGE_2 series	16ξ-Ethyl, 15-epi	80[f]	$C_{22}H_{36}O_4$	C; H[o]	2.21 × 10^{-3}	g	g
32	Ethyl ester	15ξ-Methyl	29[e]	$C_{23}H_{40}O_4$	C, H			
32'[p]	None	15ξ-Methyl	68[e,f]	$C_{21}H_{36}O_4$	C, H	6.99 × 10^{-6}	4.24 × 10^{-6}	(3.2 × 10^{-6})[h]
33	3-Oxa, ethyl ester	15ξ-Methyl	37[e]	$C_{22}H_{38}O_5$	C, H	78.8 × 10^{-6}	282 × 10^{-6}	618 × 10^{-6}
33'	3-Oxa	15ξ-Methyl	92[e,f]	$C_{20}H_{34}O_5$	C, H	121 × 10^{-6}	25.6 × 10^{-6}	73.7 × 10^{-6}
34a'[q]	None	17,17-Dimethyl				196 × 10^{-6}	316 × 10^{-6}	483 × 10^{-6}
l-PGE_1						1.07 × 10^{-6}	7.0 × 10^{-7}	3.3 × 10^{-6}

Footnotes to Table I

[a] Spectral data for all compounds are consistent with the assigned structures. See also ref 15 and 16. [b] Analyses indicated by letter only were within ±0.4% of the calculated values. [c] The broncholytic activity of each compound was measured in at least four guinea pigs for each of the three spasmogenic substances at each dose level. The median standard error for ED_{50} values was 0.3 log unit. See also Experimental Section and ref 24. [d] Yields resulting from saponification of the conjugate adducts, followed by epimeric separation at the acid stage. [e] Yields of C-15 epimeric racemates. [f] Saponification yields. [g] At 3.2 mg/kg the inhibition of bronchoconstriction was less than 50%. [h] The lowest dose providing ≥50% inhibition of constriction; a flat dose-response effect was obtained. [i] C: calcd, 72.59; found, 71.72. [j] Reference 21. [k] Product identified by TLC, IR, and ^{1}H NMR. [l] C: calcd, 71.96; found, 71.22. [m] C: calcd, 72.09; found, 71.63. [n] C: calcd, 73.43; found, 72.76. [o] H: calcd, 9.96; found, 9.38. [p] Reference 23. [q] Prepared by an analogous procedure from 3,3-dimethylpentanal; unpublished observation from these laboratories.

gem-dimethyl H). Anal. ($C_{10}H_{18}O$) H; C: calcd, 77.86; found, 77.36.

4,4-Dimethyl-3-trimethylsilyloxy-1-octyne (3). To a solution of 27 g (0.175 mol) of alcohol **2**, 34 g (0.49 mol) of imidazole, and 300 mL of DMF, cooled in an ice bath, was added slowly 26.4 g (0.245 mol) of trimethylchlorosilane. The reaction mixture was stirred at room temperature overnight and then poured into a mixture of hexane–water. The hexane layer was separated, washed with water and brine, dried, and evaporated to dryness to yield a yellow liquid. Distillation afforded 30.5 g (77%) of **3**: bp 38–40 °C (0.05 mm); IR 3225, 877, and 847 cm^{-1}; ^{1}H NMR δ 4.01 [d, 1 H, HC≡CC*H*(OSiMe$_3$)–, J = 2 Hz], 2.33 (d, 1 H, *H*C≡CCH–, J = 2 Hz), 0.92 (t, 3 H, CH_2CH_3), 0.90 (s, 6 H, *gem*-dimethyl H), and 0.16 [s, 9 H, Si(CH_3)$_3$].

(*E*)-4,4-Dimethyl-1-iodo-3-trimethylsilyloxy-1-octene (4). To a solution of 9.09 g (0.24 mol) of $NaBH_4$, 37.9 g (0.54 mol) of 2-methyl-2-butene, and 350 mL of glyme, cooled to 0 to −5 °C, was added 38.39 g (0.2 mol) of boron trifluoride etherate dropwise while maintaining the reaction mixture below 0 °C. The reaction mixture was stirred at this temperature for an additional 2 h. A solution of 30.5 g (0.135 mol) of **3** and 10 mL of glyme was then added slowly, maintaining the reaction mixture below 5 °C. The reaction mixture was then allowed to warm and stirred at room temperature for 2 h. After cooling to −5 °C, 72 g (0.95 mol) of anhydrous trimethylamine oxide was added portionwise over 10 min, maintaining the temperature at 15–20 °C. After stirring for 2 h at room temperature, the reaction mixture was added to 2390 mL of ice-cold 15% NaOH solution with simultaneous addition of a solution of 192 g of iodine and 500 mL of THF and stirred for 30 min. The organic phase was separated, and the aqueous layer was extracted with ether. The combined organic layers were washed twice with a 5% sodium thiosulfate solution (500 mL each) and brine, dried, and then evaporated to dryness. The crude material[11] was treated with 700 mL of a solution of acetic acid–THF–water (4:2:1) for 10 min, diluted with toluene, and concentrated in vacuo to give a yellow liquid, which was dry column chromatographed (silica gel; benzene) to give (*E*)-4,4-dimethyl-3-hydroxy-1-iodo-1-octene as a pale yellow liquid: IR 3400, 1605, and 950 cm^{-1}; ^{1}H NMR δ 6.66 (dd, 1 H, ICH=C*H*–, $J_{1,2}$ = 14 Hz, $J_{2,3}$ = 6 Hz), 6.28 (d, 1 H, IC*H*=CH–, J = 14 Hz), 3.76 [d, 1 H, –C*H*(OH)–, J = 6 Hz], 2.55 (m, 1 H, –OH), 0.90 (t, 3 H, $-CH_2CH_3$), 0.83 and 0.80 (s and s, 6 H, *gem*-dimethyl H).

Silylation of this material by the procedure described above for **3** furnished 19.79 g (41% from **3**) of **4** as a yellow oil: bp 72–74 °C (0.05 mm); IR 1600, 955, 885, and 845 cm^{-1}; ^{1}H NMR δ 6.56 (dd, 1 H, ICH=C*H*–, $J_{1,2}$ = 14 Hz, $J_{2,3}$ = 6 Hz), 6.08 (d, 1 H, IC*H*=CH–, J = 14 Hz), 3.52 [d, 1 H, –C*H*(OSiMe$_3$)–, J = 6 Hz], 0.91 (t, 3 H, $-CH_2CH_3$), 0.82 and 0.80 (s and s, 6 H, *gem*-dimethyl H), and 0.10 [s, 9 H, Si(CH_3)$_3$]. Anal. ($C_{13}H_{27}OISi$) C, H, I.

Ethyl 2-Methylhexanoate (16). A solution of 25 g (0.192 mol) of 2-methylhexanoic acid and 200 mL of absolute ethanol containing 400 mg of *p*-toluenesulfonic acid was refluxed under an argon atmosphere for 30 h. The solution was cooled and then evaporated to dryness in vacuo. The residual oil was dissolved in ether, washed with saturated $NaHCO_3$ and brine, dried, and evaporated to dryness. Distillation of the crude material provided 21.9 g (73%) of **16** as a colorless liquid: bp 58 °C (11 mm); IR 1742 cm^{-1}; ^{1}H NMR δ 4.10 (q, 2 H, $-OCH_2CH_3$, J = 7 Hz), 2.33 (m, 1 H, –C*H*$CO_2C_2H_5$), 1.13 (d, 3 H, $-CH_3$, J = 7 Hz), and 0.90 (t, 3 H, $-CH_2CH_3$). Anal. ($C_9H_{18}O_2$) C, H.

2-Methylhexanal (17). A solution of 9 g (56.9 mmol) of ethyl 2-methylhexanoate (**16**) in 100 mL of dry toluene was cooled to −75 °C and 75 mL (68.3 mmol) of 0.91 M diisobutylaluminum hydride was added. The solution was kept at −75 °C for 2 h before 150 mL of saturated bisulfite solution was added. The solution was allowed to warm to room temperature, solids were removed by filtration, and the layers were separated. The toluene layer was extracted twice with bisulfite which was combined with the aqueous layer, basified with 2 N NaOH to pH 8–9 (with cooling), and extracted with ether. The ether was washed with water, dried, and evaporated to give 5 g (77%) of **17** as a colorless oil: IR 2700 and 1724 cm^{-1}; ^{1}H NMR δ 9.63 (d, 1 H, CHO, J = 2 Hz), 2.30 (m, 1 H, –C*H*CHO), 1.08 (d, 3 H, $-CH_3$, J = 7 Hz), and 0.93 (t, 3 H, $-CH_2CH_3$).

3-Hydroxy-4-methyl-1-octyne (18). To a solution of 20 g (0.217 mol) of lithium acetylide–ethylenediamine complex in 160 mL of dry Me_2SO was added dropwise 15.49 g (0.1349 mmol) of 2-methylhexanal **17** in 10 mL of Me_2SO. The resulting mixture was stirred at ambient temperature for 18 h and then poured into iced HCl. The solution was extracted several times with ether. The combined extracts were washed with brine, dried, taken to dryness, and distilled to furnish 13.9 g (73%) of **18** as a pale yellow oil: bp 80–82 °C (11 mm); IR 3500, 3300, and 2105 cm^{-1}.

4-Methyl-3-trimethylsilyloxy-1-octyne (20). Silylation of **18** by the procedure described above for **3** afforded 14.3 g (67%) of **20**: bp 81–83 °C (11 mm); R_f 0.8 (benzene); IR 3300, 873, and 840 cm^{-1}; ^{1}H NMR δ 4.25 (m, 1 H, HC≡CC*H*CH–), 2.34 (d, 1 H, *H*C≡CCH–, J = 2 Hz), 0.96 (m, 6 H, $-CH_2CH_3$ and CH_3), and 0.23 [s, 9 H, (CH_3)$_3$Si]. Anal. ($C_{12}H_{24}OSi$) C, H.

4-Ethyl-3-trimethylsilyloxy-1-octyne (21). Silylation, by the procedure described above for **3**, of 4-ethyl-3-hydroxy-1-octyne (**19**) provided 64 g (97%) of 4-ethyl-3-trimethylsilyloxy-1-octyne (**21**): bp 91–93 °C (15 mm); IR 3333, 880, and 845 cm^{-1}. Anal. ($C_{13}H_{26}OSi$) C, H.

(*E*)-1-Iodo-4-methyl-3-trimethylsilyloxy-1-octene (22). Hydroboration–oxidation–iodination of **20** by the procedure described above for **4** provided 12.8 g (56%) of **22**: bp 70 °C (0.075 mm); IR 1613, 881, and 840 cm^{-1}; ^{1}H NMR δ 6.56 (dd, 1 H, ICH=C*H*CH–, $J_{1,2}$ = 14 Hz, $J_{2,3}$ = 6 Hz), 6.13 (d, 1 H, IC*H*=CH–, J = 14 Hz), 3.93 [m, 1 H, CHC*H*(OSiMe$_3$)–], 0.94 (m, 6 H, $-CH_2CH_3$ and $-CH_3$), and 0.10 [s, 9 H, (CH_3)$_3$Si]. A satisfactory analysis could not be obtained, but the material was adequate for further transformations.

(*E*)-4-Ethyl-1-iodo-3-trimethylsilyloxy-1-octene (23). Conversion of 4-ethyl-3-trimethylsilyloxy-1-octyne (**21**) to the vinyl iodide was effected by the method described above for **4**, providing 46.4 g (48%) of **23**: bp 78–80 °C (0.15 mm); IR 1600, 880, and 845 cm^{-1}; ^{1}H NMR δ 6.52 (dd, 1 H, ICH=C*H*–, $J_{1,2}$ = 14 Hz, $J_{2,3}$ = 6 Hz), 6.16 (d, 1 H, IC*H*=CH–, J = 14 Hz), 4.08 [m, 1 H, CH=CHC*H*(OSiMe$_3$)–], 0.90 (m, 6 H, $-CH_2CH_3$), and 0.18 [s, 9 H, (CH_3)$_3$Si]. Anal. ($C_{13}H_{27}OISi$) C, H, I.

(*E*)-3-Hydroxy-1-iodo-3-methyl-1-octene (30). To a Grignard solution prepared from 1.05 g (0.41 mol) of Mg and 6.2 g (0.435 mol) of methyl iodide in 30 mL of dry ether under argon was added dropwise 10 g of (*E*)-1-iodo-1-octen-3-one (**29**)[10] in 45 mL of ether. The resulting solution was stirred at ambient temperature for 1 h. After the addition of 75 mL of saturated NH_4Cl solution, the ether layer was separated and the aqueous layer was extracted several times with ether. The combined ether extracts were washed successively with NH_4Cl solution and water, dried, and taken to dryness to give 9.24 g (73%) of **63** as an oil: IR 3460, 1602, and 952 cm^{-1}.

(*E*)-1-Iodo-3-methyl-3-trimethylsilyloxy-1-octene (31). Silylation of **30** by the procedure described above for **3** afforded 14.7 g of oil. Distillation provided 13.4 g (90%) of **31** as a colorless oil: bp 65 °C (0.05 mm); IR 1610, 1250, 1111, 951, 840, and 758 cm^{-1}; ^{1}H NMR δ 6.55 (d, 1 H, CHI=C*H*–, J = 14 Hz), 6.15 (d, 1 H, C*H*I=CH–, J = 14 Hz), 0.90 (t, 3 H, $-CH_2CH_3$), and 0.10

[s, 9 H, $(CH_3)_3Si$]. Anal. ($C_{12}H_{25}IOSi$) C, H, I.

Guinea Pig Bronchodilator Assay.[1,24] Hartley guinea pigs of either sex, weighing 250–500 g, were anesthetized by intraperitoneal injection of urethane (1.5 g/kg) and given an intravenous injection of gallamine. They were artificially ventilated through a tracheal cannula (60 strokes/min), the respiratory volume being adjusted according to the weight of the animal and the rate of the pump.[28] The two jugular veins were catheterized, the first one being used for curarization and administration of the drugs and the second for the injection of the spasmogenic agent. This injection was made at different selected speeds with a perfusion pump (Braun Unita 1). The intratracheal pressure was measured with a transducer (Sanborn 267 AC) connected to the tracheal cannula and recorded on a Sanborn polygraph.

Bronchial spasms were produced by intravenous injection of acetylcholine, histamine, or serotonin. The speed of injection of the spasmogenic solution and its concentration were chosen to produce an increase of the tracheal pressure of 20–50 cm of water. For acetylcholine that dose varied from 40 to 150 μg/kg, for histamine from 5.6 to 22.5 μg/kg, and for serotonin from 7.5 to 30 μg/kg.

Injections of 12-s duration were repeated every 5 min throughout the entire assay. When three successive control bronchoconstrictions of similar intensity were obtained, the animal was considered to be ready for the assay and received the first dose of the candidate compound 2 min later.

The water-soluble compounds (sodium salts) were injected through the jugular vein. The injection required 1 min and was repeated three or four times per animal at 15-min intervals so that three of four doses, in logarithmic progression, were assayed. Water-insoluble compounds (esters) were dispersed in 10% aqueous ethanol and administered in the same way.

The broncholytic activity of each compound was measured in at least four guinea pigs for each of the three spasmogenic substances. The amplitude of the spasms (i.e., the difference between the maximum total tracheal pressure during the spasms and the normal insufflation pressure without spasm) following the administration of the drug is expressed in centimeters of water. For each spasm the mean difference vs. the control [i.e., Σ(treated spasm-control spasm)/control spasm] was calculated. For an easier expression of the results, mean difference was transformed into a percentage of variation. When the percent of variation of the first spasm following any dose of the drug reached at least −50%, a regression line of the percent of variation vs. the dose was computed in a semilogarithmic system. The ED_{50} (dose producing a −50% variation) was then calculated.

When a compound was not active enough to allow the calculation of an ED_{50}, the ED_{50} is considered to be greater than the maximal dose administered.

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(16) Compounds depicted with the 15-nat configuration are actually racemates containing 8-nat, 12-nat, 15-nat, and 8-epi, 12-epi, 15-epi diastereomers. Likewise, compounds depicted as 15-epi are actually racemates containing 8-nat, 12-nat, 15-epi, and 8-epi, 12-epi, 15-nat diastereomers.
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Dibenztroponeacetic and -propionic Acids. Potent New Antiinflammatory Agents[1]

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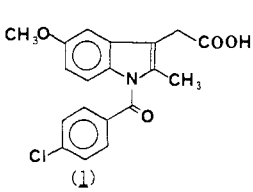
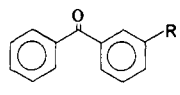
The syntheses and antiinflammatory assays of some dibenztroponeacetic and -propionic acids and derivatives are described. The most potent compound, *d*-2-(5*H*-dibenzo[*a*,*d*]cyclohepten-5-on-2-yl)propionic acid, has a potency of ca. 70 times phenylbutazone in the rat carrageenan paw assay and two to three times indomethacin in long-term animal assays. Some β-dialkylaminoethyl esters of this compound also show high antiinflammatory activity.

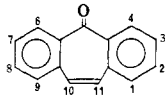
In recent years a number of arylacetic and arylpropionic acids have been reported to possess useful antiinflammatory activity. The aryl moieties in these agents show considerable structural diversity, examples of mono-,[2a] bi-,[2b] and tricyclic[3] types having been reported, including both carbocyclic and heterocyclic rings. It has also been shown that the acetic acid group can be replaced by other acidic functions such as tetrazole,[4] trifluoromethylsulfonamide,[5] or acylhydroxamic acid.[6] Using the results of conformational studies on indomethacin (**1**), Shen[7]



(**1**)



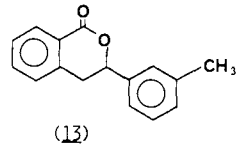
(**2**)
(a) R=CH_2COOH
(b) R=$NHSO_2CF_3$



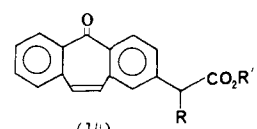
(**3**)

proposed an antiinflammatory receptor site for this molecule, a feature of which was the presence of a cavity to accommodate the *p*-chlorobenzoyl substituent, which had been shown to be twisted out of plane and out of conjugation with the indole nucleus. Subsequently a number of benzophenones substituted (usually in the meta position) with an acidic group (e.g., **2a**[8] and **2b**[5]) have been reported to show antiinflammatory activity. It is evident that these molecules and indomethacin have common structural features and that, if the unsubstituted phenyl ring in **2a** and **2b** is rotated out of coplanarity with the ring bearing the acidic group, these compounds can be accommodated by the hypothetical indomethacin receptor site. We report here the synthesis and biological activity of arylacetic acids containing the 5*H*-dibenzo[*a*,*d*]cycloheptene-5-one (dibenztropone) moiety (**3**), in which the two benzene rings are held in a noncoplanar orientation by the two-carbon bridge. However, these compounds differ from those described above in that the acidic function is para, rather than meta, to the carbonyl group. Nevertheless, as will be seen, these compounds show considerable antiinflammatory activity.

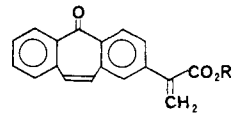
Chemistry. Attempted Friedel–Crafts acylation of the commercially available dibenztropone and the 10,11-dihydro derivative, dibenzsuberone, gave no reaction. Rather than pursue this approach, which would in any case be expected to lead predominantly to 3-substituted products, and not to the desired 2-compounds, an efficient synthesis of 2-methyldibenztropone (**4**) was developed, as shown in Scheme I. Attempts were made to cyclize the Wittig product **17**, obtained as a ca. 1:1 cis–trans mixture, directly to **4**; however, the lactone **13** was the only isolable product. The double bond was therefore removed by catalytic hydrogenation, and the product, **6**, was cyclized cleanly to **7** using polyphosphoric acid (the alternative cyclization product, 4-methyldibenzsuberone, was not formed in appreciable amounts). After introduction of the double bond by *N*-bromosuccinimide bromination followed by dehydrobromination, the benzylic bromide **8a** was produced by treatment of **4** with *N*-bromosuccinimide. Conversion of **8a** to the nitrile **8b** proceeded in only moderate yield and was accompanied by many side reactions which complicated isolation of the product. After extensive experimentation it was found that the highest yield was obtained by using sodium cyanide in acetone cyanohydrin. However, the process was far from ideal, and methods were sought for protection of the 5-ketone in **8a**, to the presence of which were ascribed the side reactions in the formation of **8b**. Ketalization of dibenztropones is difficult,[9] and since the labile bromide in **8a** would not survive the forcing conditions necessary, an alternative, milder method was required. Treatment of **8a** with 1 mol of phosphorus pentachloride in benzene at room temperature gave a solution presumed to contain the equilibrium mixture of **9a** and **9b**[10] (the solution was colorless in benzene, but pink in acetonitrile, indicating a greater proportion of the ionized form **9a** in the more polar solvent). The solution of **9** was then added to a mixture of ethylene glycol, triethylamine, and acetonitrile to give a high yield of the ketal **10**, from which the bromide could be cleanly displaced with cyanide ion to give **11**; acid hydrolysis then afforded the acetic acid **12**. Alkylation of the lithio anion of the methyl ester of **12** with methyl iodide or, respectively, ethyl iodide gave after base hydrolysis the propionic acid **14a** and the butyric acid **14b**. Treatment of the anion with formaldehyde vapor gave a low yield of the acrylic ester **15a**; larger quantities were produced by treatment of the ester **14c** with *N*-bromosuccinimide to give **16a** which on treatment with silver



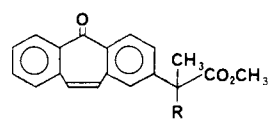
(**13**)



(**14**)
(a) R=CH_3 R'=H
(b) C_2H_5 H
(c) CH_3 CH_3



(**15**)
(a) R=CH_3
(b) H



(**16**)
(a) R=Br
(b) OH

perchlorate in aqueous acetone gave approximately equal